

Remarks

Claims 30, 39, 44, 49, and 52 are pending. Claims 50 and 51 have been withdrawn from further consideration by the Examiner and are canceled without prejudice to prosecute these claims in a continuing application.

Election/Restrictions

Claims 30, 39, 44, and 49-52 have been restricted under 35 U.S.C. § 121 as follows:

- I. Claims 30, 39, 44, 49, and 52 are said to be drawn to a method of treating a neoplastic disease with the compound of formula I, II, or a compound of claim 49;
- II. Claim 33 is said to be drawn to a method of inducing cytokine biosynthesis with the compound of claim 49.
- III. Claim 34 is said to be drawn to a method of treating a viral disease with the species compound of claim 49.

Applicants thank Examiner Huang for the telephone conversation on April 30, 2004 with the undersigned, wherein the Examiner presented a restriction requirement including groups I, II, and III, and the undersigned made an election of group I with traverse.

Applicants hereby affirm the election of Group I.

§ 112 Rejections

Claims 30, 39, 44, and 52 stand rejected under 35 USC § 112, first paragraph, allegedly as failing to comply with the enablement requirement, allegedly because the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the claimed invention without undue experimentation.

This rejection is traversed. Reconsideration and removal of this rejection is respectfully requested.

As an initial matter, Applicants submit that the analysis in the Office Action is burdened by a mischaracterization of the art. The Office Action characterizes the scope of the art for purposes of the analysis as the anticancer art. Applicants respectfully submit that characterizing the

art in this way includes a large volume of art, the state of which is immaterial to the presently claimed invention (e.g., chemotherapy, radiation therapy, etc.) Applicants submit that the proper scope of the art is anticancer immunotherapy.

Applicants first address the Examiner's analysis under "State of the prior art and the level of skill in the art". The Office Action asserts that a nexus between the interferon biosynthesis and the treatment of neoplastic diseases has not been fully established. The Office Action provides no support for this position. However, in recent years, much has been learned in this arena. In particular, treatment with interferon alpha (IFN- α) and treatment by induction of the biosynthesis of IFN- α and other cytokines have been shown to be effective in treating neoplastic diseases in animal models and in clinical use.

For example, the use of an IFN- α product (Intron[®] A, Physicians' Desk Reference[®] (2001)) is effective for hairy cell leukemia, malignant melanoma, and follicular lymphoma. Another IFN- α product is effective for hairy cell leukemia and chronic myelogenous leukemia (Roferon[®] A, Physicians' Desk Reference[®] (2001)). IFN- α has been used effectively in treating basal and squamous cell carcinomas. (Urosevic, M., et al., "Immunotherapy for Nonmelanoma Skin Carcinoma", Cancer, Vol. 94, No. 1, 1-9, (January 1, 2002), Greenway, H. T., et al., "Treatment of basal cell carcinoma with intralesional interferon", J. Am. Acad. Dermatol., Volume 15, Number 6, 437-443 (September 1986), and Buechner, S. A., et al., "Regression of Basal Cell Carcinoma by Intralesional Interferon-alpha Treatment Is Mediated by CD95 (Apo-1/Fas)-CD95 Ligand-induced Suicide", J. Clin. Invest., Volume 100, Number 11, 2691-2696 (December 1997))

Brassard et al., *J. Leukocyte Biology*, 71, 565-581 (2002), a review, states that "Interferon- α (IFN- α) has proven to be a clinically effective antiviral and antineoplastic therapeutic drug for more than 16 years. During this time, evidence from in vitro laboratory studies and the clinical arena has supported the concept that IFN- α is an immunotherapeutic drug. By regulating a diverse set of cytokines and their receptors, IFN- α is uniquely positioned to prime the host immune response and provide an effective antineoplastic- and antiviral-immune response." This review also points out that IFN- α has been used with success to treat melanoma, Hairy Cell Leukemia, and chronic myelogenous leukemia.

Treatment of neoplastic diseases by induction of the biosynthesis of IFN- α and other cytokines has been shown to be effective. For example, antitumor activity of the immune response

modifier, imiquimod (1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine), has been shown in a number of transplantable mouse tumor models, including MC-26 colon carcinoma, B16-F10 melanoma, Lewis lung carcinoma, FCB bladder carcinoma, RIF-1 sarcoma, MBT-2 bladder cell carcinoma, and human mammary tumor MCF-7. This activity is mediated by drug induced IFN- α , not directly by the drug. See R. L. Miller et al., "Imiquimod applied topically: a novel immune response modifier and new class of drug", International Journal of Immunopharmacology, 21, 1-14 (1999). In clinical use, imiquimod was effective in treating basal cell carcinoma. See Karl R. Beutner, MD, et al., "Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream", J. Am. Acad. Dermatol., Volume 41, Number 6, 1002-1007 (December 1999). In another example of clinical use, cutaneous metastases of malignant melanoma was successfully treated with imiquimod. See Alexander Steinmann et al., "Topical Imiquimod Treatment of a Cutaneous Melanoma Metastasis", J. Am. Acad. Dermatol., Letters, 555-556 (September 2000). In another example of clinical use, vulvar intraepithelial neoplasia was effectively treated with imiquimod. See Davis et al., "Self-Administered Topical Imiquimod Treatment of Vulvar Intraepithelial Neoplasia", Journal of Reproductive Medicine, Volume 45, Number 8, 619-623, (August 2000).

More recently, even further substantiation has been provided. For example, imiquimod 5% cream has been approved for treating basal cell carcinoma and actinic keratosis. There have been reports of successful treatments of other neoplastic diseases with this available immune response modifier, such as invasive squamous cell carcinoma and intraepithelial penile carcinoma.

Applicants, therefore, submit that a strong nexus has been established between the induction of interferon biosynthesis and the treatment of neoplastic diseases.

In addressing the analysis in the Office Action under "Predictability/unpredictability of the art", Applicants point out that the Office Action cites documents that predate the development of anticancer immunotherapy. Instead, the cited documents relate to drugs/compounds that act directly on tumors or tissue cultures, and are not related to immune response modifiers and anticancer immunotherapy. Consequently, such drugs/compounds are more likely to have a limited spectrum of activity because such drugs/compounds depend on disrupting one or more cellular mechanisms of the tumor cells for their activity. In contrast, immunotherapy does not depend on disrupting cellular mechanisms within the tumor cells, but instead induce activity of healthy cells of

the immune system to eliminate or slow the growth of tumor cells. As a result, immunotherapies such as induction of IFN- α can, as demonstrated above, have broad spectrum activity against tumors having different cellular origins and arising from different cellular mechanisms. Because the art cited in the Office Action does not pertain to anticancer immunotherapy, the cited art provides no basis for evaluating the predictability of the art to which the invention pertains.

In addressing the analysis in the Office Action under "Amount of guidance/working examples" and "Quantitation of undue experimentation", Applicants have established the nexus between induction of IFN- α and the anti-neoplastic activity of the compounds. With that nexus established, demonstration that the compounds induce IFN- α production is sufficient to establish their use in treating a neoplastic disease. Guidance for this assessment is fully provided in the specification, which provides a large number of Examples showing the ability of the compounds to induce the biosynthesis of IFN- α . Thus, ample instruction is provided to demonstrate IFN- α induction over the full scope of the claimed methods. Assays for determining the ability of a compound to induce cytokine biosynthesis, including the assays described in the specification, are well known and routinely used by those skilled in the art. Additionally, the specification provides dosage levels and dosage forms (at page 43) for administering the compounds. Therefore, no more than routine experimentation is required to practice the claimed invention.

In the Examiner's analysis under "Breadth of claims", the Office Action asserts that Applicants' assertion, that structurally diverse compounds are effective in treating neoplastic diseases, is not commensurate with the scope of objective enablement. However, this analysis is burdened by the over-inclusive characterization of the art as "anticancer" rather than the more relevant "anticancer immunotherapy". Moreover, as demonstrated above, structural diversity is not relevant for immunotherapy so long as the compounds possess adequate immune-stimulating activity. Applicants have demonstrated the requisite immune-stimulating activity of the compounds and provided methods for routine screening of compounds to identify those having the desired immune-stimulating activity.

Given the level of skill in the art and in view of the discussion above, sufficient direction and guidance has been provided in the specification for one skilled in the art to practice the full scope of the methods as claimed for treating a neoplastic disease, using the compounds of the present invention, without undue experimentation. Accordingly, Applicants respectfully submit

that the 35 U.S.C. § 112, first paragraph, rejection has been overcome and request that the rejection be withdrawn from claims 30, 39, 44, and 52.

Double Patenting

Claims 30, 39, 44, 49, and 52 stand rejected under obviousness-type double patenting over claims 1-12, 17-24, and 29-34 of U.S. Patent Nos. 6,664,264 and claims 1-11, 23, 24-27, 33-35, and 40-45 of 6,667,312. Claims 30, 39, 44, 49, and 52 stand provisionally rejected under obviousness-type double patenting over claims 22, 26, 31, 32, and 35 of U.S. Application No. 10/696,684. Included herewith is a terminal disclaimer in compliance with 37 CFR 1.321(c) and 37 CFR 3.73(b). Applicants, therefore, respectfully request that this rejection be withdrawn.

In view of the above, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested.

Allowance of claims 30, 39, 44, 49, and 52 at an early date is solicited.

Respectfully submitted,

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Date

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